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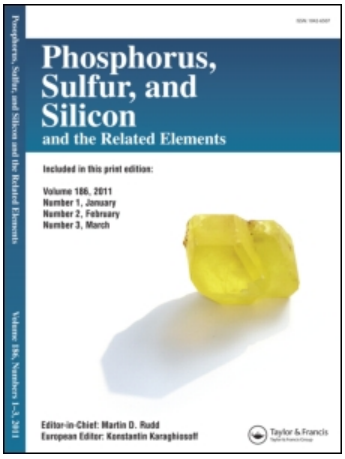

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CHIRAL VARIANTS OF ARYLALKYL SULFUR REAGENTS. (R)-CAMPHOR KETIMINES OF OGIOVANNA AMINOTHIOETHERS AND OXIDES

Giovanna Delogu[a]; Ottorino De Lucchi[b]; Maria Paola Fois[b]; Giovanni Valle[c]
[a] Istituto CNR per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, Sassari, Italy [b] Dipartimento di Chimica dell, 'Università, Sassari, Italy [c] Centro Studi Biopolimeri del CNR, Padova, Italy

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CHIRAL VARIANTS OF ARYLALKYL SULFUR REAGENTS. (*R*)-CAMPHOR KETIMINES OF *o*-AMINOTHIOETHERS AND OXIDES

GIOVANNA DELOGU,[a] OTTORINO DE LUCCHI,†[,b] MARIA PAOLA FOIS,[b] and GIOVANNI VALLE‡[c]

[a]*Istituto CNR per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, via Vienna 2, I-07100 Sassari, Italy*
[b]*Dipartimento di Chimica dell'Università, via Vienna 2, I-07100 Sassari, Italy*
[c]*Centro Studi Biopolimeri del CNR, via Marzolo 1, I-35131 Padova, Italy*

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Ketimines **1a–d** derived from *ortho*-aminosubstituted phenylthioethers were prepared in order to determine the degree of chirality transfer from the chiral auxiliary to the sulfur atom in the formation of the sulfoxide or to the α-carbon atom in the reaction of the anion with alkyl halides or benzaldehyde. Oxidation to the sulfoxide occurred with little or no asymmetric induction. The crystalline benzyl sulfone **4c** was deprotonated by alkyllithium or Grignard reagents and reacted with alkyl halides and benzaldehyde, in all cases with little to fair transfer of chirality. The major diastereoisomer from methylation of the anion of **4c** with methyl iodide, was isolated, and afforded the enantiomerically pure amine **5** after removal of the chiral auxiliary. An X-ray structure determination of **4d** allowed the assignment of the absolute configuration of the asymmetric carbon and revealed that the conformation of the ketimine in the crystal state is not homogeneous.

Key words: (*R*)-Camphor ketimines of *o*-aminothioethers; oxidation to sulfoxides; X-ray structure of sulfone **4d**.

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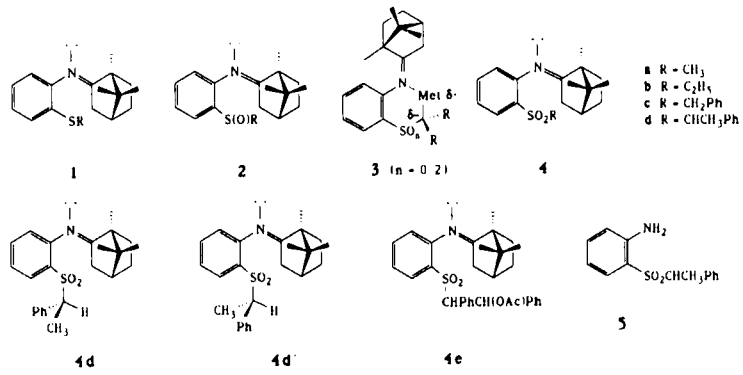
We have recently described the preparation and the Diels-Alder reaction of optically active sulfoxides prepared via an intramolecular transfer of chirality and we have shown that the auxiliary can synergically contribute to the efficiency of the chiral sulfoxide in asymmetric reactions.[1] In our interest to determine new effective reagents of this type, we have prepared a few chiral ketimines of type **1** and we have studied the transfer of chirality from the camphor auxiliary in the oxidation to the sulfoxides and in the reaction of the anion with electrophiles. We have considered aryl substituted sulfides because we wanted to avoid complexity from competition of reactions occurring at both sides of the sulfur atom and because the UV absorption of the aryl substituent allows rapid detection (TLC, HPLC, etc.) of the purity of the products.

Ketimines **1a–d** are readily prepared from the corresponding *o*-aminothioether[2] and (*R*)-camphor in refluxing toluene or cyclohexane and molecular sieves.[3] The reaction of the *o*-thioether is faster and cleaner than the corresponding aniline suggesting anchimeric assistance by the sulfur atom in the formation of the intermediate carbocation. The ketimines, in solution, appear

† Author to whom all correspondence should be addressed.
‡ Author to whom inquiries concerning the X-ray crystal structure analysis should be directed.



from the 200 MHz ^{1}H NMR data to be constituted of a single stereoisomer, supposedly the *E* conformer, as it has been suggested in other cases.[4]

The oxidation of **1a–c** with *m*-chloroperbenzoic acid affords a mixture of diastereomeric sulfoxides in *ca.* 6:4 ratio in all tested cases. In the case of the benzyl derivative **1c**, no effect on the change of solvent, temperature or type of oxidant (sodium metaperiodate, *t*-BuOOH and $MoOAcac_2$) could be noted.

Next, the study of the transfer of chirality to the carbon alpha to the sulfur atom was undertaken. Conceptually, it was conceived that, under proper reaction conditions, the sulfur-stabilized carbanion could possess a rigid structure by virtue of the interaction of the counterion with the lone pair electrons of the imine nitrogen (e.g. structure **3** or analog structures with the negative charge on the oxygen atom[5]). It was hoped that the reaction could have produced sufficiently stereo-differentiating prochiral faces as it was observed in related systems.[4,6] In order to test the hypothesis, the cristalline sulfone **4c** was prepared and reacted with *n*-butyllithium to obtain the corresponding anion. Quenching the latter with benzaldehyde, followed by acetic anhydride, afforded a 1:2:2:3 mixture of the four possible diastereoisomers **4e**.

Methylation of the anion derived from reaction of **4c** with *n*-butyllithium afforded a 2:1 mixture of diastereoisomers **4d** and **4d'**. A 1:1 mixture of the same diastereoisomers **4d** and **4d'** was also obtained via oxidation of **1d**, which in turn was obtained from the corresponding *o*-aminothioether and camphor. The two diastereoisomers could be separated by flash chromatography on silica gel and separately analyzed. When individually treated in the same conditions in which the anion was generated from **4c**, both **4d** and **4d'** restored the same diastereomeric ratio. This observation suggests that even if the alkylation occurs diastereoselectively, the two diastereoisomers equilibrate under the reaction conditions, to the finally observed mixture.

To the isomer which is formed in the higher amount has been assigned structure **4d** because generated by the least sterically hindered anion **3** (where R = H, R' = Ph). Definite structure proof was obtained by X-ray analysis. Figure 1 shows a comparative view of the ORTEP drawings of the two conformers composing the crystal lattice, while Figure 2 illustrates the arrangement in the crystal cell.

Because the camphor auxiliary has an absolute *R* configuration, the configuration of the newly generated asymmetric carbon results as *S*. It should be noticed

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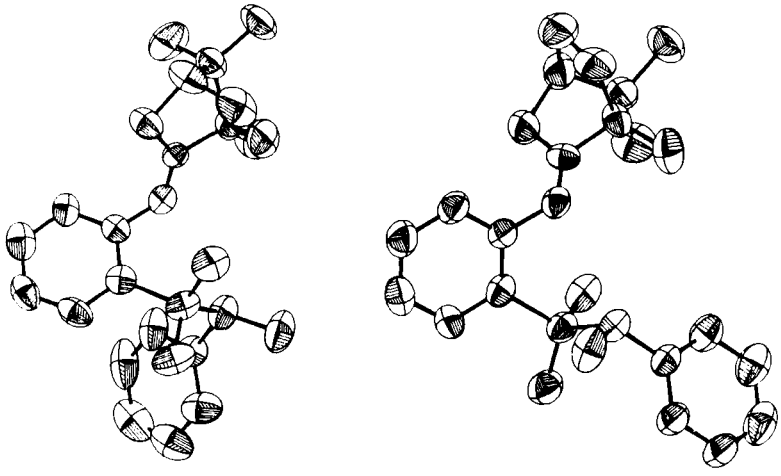

FIGURE 1 Comparative view of the ORTEP drawings of the two conformers of **4d** composing the crystal lattice. Hydrogen atoms have been omitted.

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that, as expected, in the crystal state the imine double bond is in a *E* configuration in both conformers. On the other hand, the fact that two conformations are observed, suggests that there is almost free rotation along the two bonds flanking the sulfur atoms, even in the presence of the bulky sulfone group. This observation may account for the small diastereoselection observed.

Hydrolysis of the ketimine in an aqueous solution of citric acid gave the optically active amine **5** in high yield, showing that the route is a viable method for the synthesis otherwise difficultly accessible chiral molecules.

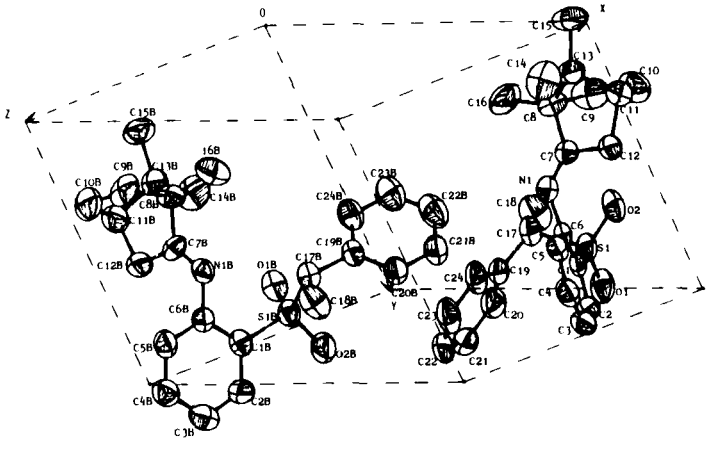

FIGURE 2 Perspective drawing with atom labelling of the two conformers of **4d**, as assembled in the crystal cell. Hydrogen atoms have been omitted.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP200SY or a Varian EM360A spectrometers. IR spectra were recorded on a Perkin–Elmer 983 spectrometer. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter in $CHCl_3$ solutions (1 dm cell). Microanalysis were performed by Mr. Antonello Canu in the Department of Chemistry of the University of Sassari. Commercially available *m*-chloroperbenzoic acid (Aldrich) was used without further purification. *t*-Butyl hydroperoxide and benzaldehyde were distilled under nitrogen before use. The silica-alumina catalyst (Catalyst Base 32-300, Union Carbide) had the following specifications: surface area 717 m^2/g and Al_2O_3 content 23.6 wt%. The *o*-aminothioethers **1a–d** used in this research were prepared according to literature procedures and purified to match the reported physical and spectral data.[2]

General procedure for the preparation of ketimines **1a–d**. A toluene or cyclohexane solution (ca. 80 ml) of (+)-1*R*,4*R*-camphor (0.10 mol) and *o*-aminophenylthioether (0.12 mol), containing molecular sieves (pellets, 5 Å, 32 g) and silica-alumina catalyst (8 g), was refluxed for 48 h. The suspension was filtered and the sieves were thoroughly washed with several portions of cyclohexane. The solvent was removed and the residue crystallized from *n*-pentane.

1a (80% yield): mp 50–4°C, $[\alpha]^{25} = +32.0°$ ($c = 1.00$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.91 (3H, s), 0.97 (3H, s), 1.14 (3H, s), 1.28 (1H, m), 1.55–1.96 (4H, series of m), 1.71 (1H, d, J 17.5 Hz), 2.15 (1H, dm, J 17.5), 2.40 (3H, s), 6.62 (1H, m), 6.97–7.19 (3H, m). IR (KBr pellets), ν_{max} 1675 (C=N), 737 (S–R) cm^{-1}. (Found: C, 74.3; H, 8.7; N, 5.2. $C_{17}H_{23}NS$ requires C, 74.6; H, 8.5; N, 5.2%).

1b (70% yield): mp 55–6°C, $[\alpha]^{25} = +20.47°$ ($c = 1.05$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.92 (3H, s), 0.97 (3 H, s), 1.13 (3H, s), 1.29 (3H, t, J 7.3 Hz), 1.54–2.00 (5H, series of m), 1.69 (1H, d J 17.7 Hz), 2.15 (1 H, dm, J 17.7 HZ), 2.89 (2H, q, J 7.3 Hz), 6.62 (1H, dd, J 7.3 and 1.8 Hz), 6.99 (1H, td, J 7.3 and 1.8 Hz), 7.10 (1H, td, J 7.3 and 1.5 Hz), 7.27 (1 H, dd, J 7.3 and 1.5 Hz). IR (KBr pellets), ν_{max} 1674 (C=N), 778 (S-R) cm^{-1}. (Found: C, 75.4; H, 9.0; N, 5.0. $C_{18}H_{25}NS$ requires C, 75.2; H, 8.8; N, 4.9%).

1c (98% yield): oil, $[\alpha]^{25} = +17.43°$ ($c = 1.04$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.92 (3 H, s), 0.97 (3H, s), 1.17 (3H, s), 1.56–1.91 (5H, series of m), 1.69 (1H, d, J 17.7 Hz), 2.15 (1H, dm, J 17.7 Hz), 4.09 (2H, s), 6.66 (1 H, dd, J 7.6 and 1.5 Hz), 6.94 (1H, td, J 7.6 and 1.5 Hz), 7.12. (1H, td, J 7.6 and 1.5 Hz), 7.18–7.35(6H, m). IR (KBr pellets), ν_{max} 1684 (C=N), 780 (S–R) cm^{-1}.

1d (98% yield): oil from flash chromatography eluting with 9:1 petrol ether-ethyl acetate; 1:1 mixture of two diastereoisomers. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.91 (3H, s, one diast.), 0.95 (3 H, s, one diast.), 0.98 (3H, s, two diast.), 1.18 (3H, s, two diast.), 1.51–1.92 (5H, series of m, two diast.), 1.55 (3H, d, 7.0 Hz, one diast. $SCHCH_3$), 1.56 (1H, d, J 7.0 Hz, one diast. $SCHCH_3$), 1.65 (1H, d, J 17.7 Hz, one diast.), 1.66 (1 H, d, J 17.7 Hz, one diast.), 2.13 (1H, dm, J 17.7 Hz, two diast.), 4.52 (1 H, q, J 7.0 Hz, one diast.), 4.53 (1H, q, J 7.0 Hz, one diast.), 6.64 (1H, dd, J 7.5 Hz, two diast.), 6.87 (1 H, dt, J 7.5 Hz, two diast.), 7.05–7.38 (7H, m, 2 diast.). IR (KBr pellets), ν_{max} 1684 (C=N), 781 (S–R) cm^{-1}.

General procedure for the oxidation to the sulfoxide with m-chloroperbenzoic acid. A dichloromethane solution of *m*-chloroperbenzoic acid (85%) was added dropwise to a stirred and cooled (−5°C, ice-salt bath) solution of the equimolar quantity of the sulfide (*ca.* 2–3 mmol) in the same solvent. The reaction temperature was kept at −5°C for 2–3 h or until disappearance of the peroxide. The resulting white suspension was washed with aqueous sodium sulfite and 5% sodium carbonate. The organic layer was dried over anhydrous sodium sulfate and evaporated. Pure material was obtained after flash-chromatography on silica gel, eluting with a *ca.* 1:1 mixture of petrol ether-ethyl acetate.

2a (90% yield): oil, 3:2 mixture of two diastereoisomers. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.86 (3H, s, one diast.), 0.87 (3H, s, one diast.), 0.97 (3H, s, two diast.), 1.05 (3H, s, one diast.), 1.06 (3H, s, one diast.), 1.12–1.97 (5H, series of m, two diast.), 1.68 (1H, d, J17.5 Hz, one diast.), 1.87 (1H, d, J 17.5 Hz, one diast.), 2.12 (1H, dm, J 17.5 Hz, one diast.), 2.35 (1H, dm, J 17.5 Hz, one diast.), 2.82 (3H, s, one diast.), 2.85 (3H, s, one diast.), 6.66 (1H, dd, two diast.), 7.2–7.4 (2H, series of m, two diast.), 7.78–8.05 (1H, series of m, two diast.).

2b (95% yield): oil, 1:1 mixture of two diastereoisomers. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.87 (3H, s, one diast.), 0.89 (3H, s, one diast.), 0.98 (3H, s, one diast.), 0.99 (3H, s, one diast.), 1.09 (3H, s, one diast.), 1.13 (3H, s, one diast.), 1.21 (3H, t, J 7.0 Hz, one diast.), 1.26 (3H, t, J 7.0 Hz, one diast.), 1.44–2.01 (6H, series of m, two diast.), 2.16 (1H, dm, J17.7 Hz, one diast.), 2.36 (1H, dm, J 17.7 Hz, one diast.), 2.88–3.30 (two diastereotopic H, complex m, two diast.),

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6.73 (1H, dd, *J* 7.3 and 1.8 Hz, one diast.), 6.75 (1H, dd, *J* 7.3 and 1.8 Hz, one diast.), 7.25–7.46 (2H, series of m, two diast.), 7.80 (1H, dd, *J* 7.3 and 1.8 Hz, two diast.), 7.83 (1H, dd, *J* 7.3 and 1.8 Hz, two diast.).

2c (95% yield): oil, 1:1 mixture of two diastereoisomers. ^{1}H NMR (60 MHz, $CDCl_3$, TMS) δ (ppm): 0.84 (3H, s, one diast.), 0.87 (3H, s, one diast.), 0.92 (3H, s, one diast.), 0.95 (3H, s, one diast.), 1.00 (3H, s, one diast.), 1.15 (3H, s, one diast.), 1.08–2.19 (6H, series of m, two diast.), 2.39 (1H, dm, *J* 17.7 Hz, two diast.), 4.00 (1H, d, *J* 12.7 Hz, one diast.), 4.04 (1H, d, *J* 12.7 Hz, one diast.), 4.45 (1H, d, *J* 12.7 Hz, two diast.), 6.52–6.92 (2H, series of m, two diast.), 6.92–7.71 (7H, series of m, two diast.).

Oxidation of **1a** *with t-butyl hydroperoxide.* To a cooled (−15°C) solution of **1a** (95 mg, 0.347 mmol) and $MoOAcac_2$ (3.4 mg, 0.010 mmol) in 5 ml of methanol was added *t*-butyl hydroperoxide (31.7 mg, 0.347 mmol). After stirring 50 min, the solution was washed with aqueous sodium sulfite and rotoevaporated to dryness. A colorless oil of the two diastereoisomers **2a** (60 mg, 60% yield) was obtained by flash-chromatography on silica gel eluting with a gradient petrol ether-ethyl acetate.

Oxidation of **1c** *with sodium metaperiodate.* To a solution of **1c** (500 mg, 1.43 mmol) in 3 ml of methanol was added, at 0°C, a 10% aqueous solution of sodium metaperiodate (3.05 ml, 1.43 mmol) and the resulting suspension was stirred at ice temperature for 2 h. The reaction mixture was slowly allowed to reach room temperature overnight, added of water and extracted with dichloromethane. The organic layer was dried (anhydrous Na_2SO_4) and evaporated in vacuo. The residue was separated by column chromatography on silica gel eluting with a gradient petrol ether-ethyl acetate to afford **2c** in 90% yield.

Preparation of sulfones. To a dichloromethane solution of the ketimine (1 equiv.) was added dropwise a 4% solution of *m*-chloroperbenzoic (2.1 equiv.) in the same solvent. The resulting mixture was stirred at room temperature for 5–6 h or until disappearance of the ketimine (TLC). After addition of aqueous sodium sulfite and sodium carbonate and extraction with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was recrystallized from the appropriate solvent.

4a (98% yield): mp 118–120°C (EtOH), $[\alpha]^{25} = -55.24°$ ($c = 1.01$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.73–0.90 (1H, m), 0.94 (3H, s), 0.99 (3H, s), 1.10 (3H, s), 1.12–1.43 (1H, m), 1.65–1.98 (3H, series of m), 1.83 (1H, d, *J* 17.5 Hz), 2.28 (1H, dm, *J* 17.5 Hz), 3.23 (3H, s), 6.74 (1H, dd, *J* 7.9 and 1.2 Hz), 7.18 (1H, td, *J* 7.9 and 1.2 Hz), 7.51 (1H, td, *J* 7.9 and 1.5 Hz), 8.01 (1H, dd, *J* 7.9 and 1.5 Hz). IR (KBr pellets), ν_{max} 1687 (C=N), 1300 (SO_2 asymm. stretch.), 1141 (SO_2 symm. stretch.) cm^{-1}. (Found: C, 66.4; H, 7.4; N, 4.5. $C_{17}H_{23}NO_2S$ requires C, 66.8; H, 7.6, N, 4.6%).

4c (60% yield): mp 118–120°C (petrol ether), $[\alpha]^{25} = -100.9°$ ($c = 1.052$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.99 (3H, s), 1.02 (3H, s), 1.20 (3H, s), 1.34 (1H, m), 1.73–2.00 (5H, m), 2.33 (1H, dm, *J* 17.7 Hz), 4.63 (1 H, 1/2AB *J* 13.4 Hz), 4.71 (1 H, 1/2AB, *J* 13.4 Hz), 6.75 (1 H, dd, *J* 7.6 and 1.2 Hz), 7.03 (1H, td, *J* 7.6 and 1.2 Hz), 7.26 (5H, m), 7.47 (1H, td, *J* 7.6 and 1.2 Hz), 7.69 (1H, dd, *J* 7.6 and 1.2 Hz). IR, (KBr pellets), ν_{max} 1679 (C=N), 1322 (SO_2 asymm. stretch.), 1145 (SO_2 symm. stretch.) cm^{-1}. (Found: C, 72.2; H, 7.4; N, 3.7. $C_{23}H_{27}NO_2S$ requires C, 72.4; H, 7.1; N, 3.7%).

4d and **4d'** (98% yield): The two diastereoisomer were separated by flash-chromatography eluting with petrol ether—ethyl acetate, 95:5. **4d**: mp 120–2°C (EtOH), $[\alpha]^{25} = -17.53°$ (c = 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.97 (3H, s), 1.02 (3H, s), 1.20 (3H, s), 1.23–1.45 (1H, m), 1.74 (3H, d, *J* 7.0 Hz), 1.69–1.97 (5H, m), 2.32 (1H, dm, *J* 17.5 Hz), 5.07 (1H, q, *J* 7.0 Hz), 6.68 (1H, dd, *J* 7.3 and 1.2 Hz), 6.95 (1 H, td, *J* 7.3 and 1.2 Hz), 7.15–7.45 (6H, m), 7.59 (1H, dd, *J* 7.3 and 1.2 Hz). **4d'**: oil, $[\alpha]^{25} = +87.97°$ (c = 0.158, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 0.98 (3H, s), 1.01 (3H, s), 1.22 (3H, s), 1.18–1.36 (1H, m), 1.61 (3H, d, *J* 7.0 Hz), 1.73–1.96 (5H, m), 2.30 (1H, dm, *J* 17.5 Hz), 5.09 (1H, q, *J* 7.0 Hz), 6.72 (1H, dd, *J* 7.9 and 1.8 Hz), 7.08 (1H, td, *J* 7.9 and 1.8 Hz), 7.25–7.52 (6H, m), 7.81 (1H, dd, *J* 7.9 and 1.8 Hz. IR (KBr pellets), ν_{max} 1672 (C=N), 1625 (C=N), 1303 (SO_2 asymm. stretch.), 1291 (SO_2 asymm. stretch.), 1137 (SO_2 symm. stretch.), 1128 (SO_2 symm. stretch.) cm^{-1}. (Found: C, 72.5; H, 7.8; N, 3.5. $C_{24}H_{29}O_2NS$ requires C, 72.8; H, 7.3; N, 3.5%).

General procedure for the generation of the carbanion and reaction with electrophiles. To a solution of sulfone **4c** (1 mmol.) in absolute THF (2 ml), cooled at −78°C and under a nitrogen atmosphere, was added dropwise via syringe *n*-butyllithium (1.5 M in hexane, 1.1 mmol). The solution was kept stirring at −78°C for 2 h and the equimolar quantity of the electrophile (benzaldehyde or methyl iodide) was added. After stirring at −78°C for additional 2 h, the solution was allowed to stand

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TABLE I

Positional parameters and equivalent U values for **4d**.

Atom	x	y	z	U_e
S(1)	0.9175(0)	0.7500(0)	0.2500(0)	557(05)
O(1)	1.0047(3)	0.8647(5)	0.3552(5)	793(18)
O(2)	0.9243(3)	0.6476(4)	0.0924(5)	701(17)
N(1)	0.7019(3)	0.5971(4)	0.0576(5)	497(16)
C(1)	0.8222(3)	0.8331(5)	0.2029(5)	476(17)
C(2)	0.8443(5)	0.98101(6)	0.2668(6)	633(23)
C(3)	0.7722(5)	1.0490(6)	0.2305(7)	676(24)
C(4)	0.6790(5)	0.96734(6)	0.1302(8)	693(28)
C(5)	0.6558(4)	0.8191(6)	0.0685(6)	539(23)
C(6)	0.7270(3)	0.7485(5)	0.1022(5)	435(19)
C(7)	0.6837(3)	0.5125(4)	−0.0964(5)	423(16)
C(8)	0.6624(4)	0.3495(5)	−0.1499(7)	576(20)
C(9)	0.7624(4)	0.3242(7)	−0.1892(10)	942(32)
C(10)	0.7650(5)	0.3588(8)	−0.3482(11)	998(34)
C(11)	0.6689(5)	0.3970(6)	−0.3910(7)	736(24)
C(12)	0.6835(4)	0.5491(5)	−0.2562(6)	662(22)
C(13)	0.5962(4)	0.2997(5)	−0.3370(7)	611(21)
C(14)	0.4962(4)	0.3330(7)	−0.3382(10)	935(33)
C(15)	0.5763(5)	0.1368(6)	−0.4375(10)	960(29)
C(16)	0.6297(6)	0.2885(7)	−0.0259(9)	1038(36)
C(17)	0.8748(4)	0.6470(6)	0.3760(6)	558(18)
C(18)	0.9491(5)	0.5633(8)	0.4105(9)	924(36)
C(19)	0.8539(4)	0.7469(5)	0.5323(6)	572(21)
C(20)	0.9269(4)	0.8153(7)	0.6886(7)	763(26)
C(21)	0.9089(6)	0.9077(7)	0.8275(9)	951(31)
C(22)	0.8198(7)	0.9383(7)	0.8144(9)	933(40)
C(23)	0.7449(6)	0.8714(8)	0.6636(10)	936(40)
C(24)	0.7637(4)	0.7735(6)	0.5216(7)	695(26)
S(1B)	0.3778(10)	0.8029(1)	0.8102(1)	524(04)
O(1B)	0.4049(2)	0.6835(4)	0.8449(4)	662(15)
O(2B)	0.4558(3)	0.9267(4)	0.8338(5)	779(17)
N(1B)	0.1750(3)	0.6346(4)	0.8157(5)	496(15)
C(1B)	0.3017(3)	0.8660(5)	0.9444(6)	509(19)
C(2B)	0.3340(4)	1.0075(5)	1.0602(6)	662(21)
C(3B)	0.2797(5)	1.0609(6)	1.1713(7)	753(24)
C(4B)	0.1912(5)	0.9727(6)	1.1649(7)	712(28)
C(5B)	0.1576(5)	0.8351(5)	1.0512(7)	597(22)
C(6B)	0.2114(3)	0.7761(5)	0.9396(6)	501(8)
C(7B)	0.1639(3)	0.5289(5)	0.8643(6)	478(19)
C(8B)	0.1179(4)	0.3739(6)	0.7430(7)	562(22)
C(9B)	0.0141(4)	0.3397(7)	0.7760(11)	830(36)
C(10)	0.0359(6)	0.3276(8)	0.9536(13)	1032(43)
C(11)	0.1503(6)	0.3635(7)	1.0062(9)	757(31)
C(12B)	0.1903(5)	0.5254(6)	1.0438(8)	677(27)
C(13B)	0.1735(4)	0.2910(6)	0.8362(8)	617(25)
C(14B)	0.2832(5)	0.3262(9)	0.8424(12)	901(39)
C(15B)	0.1300(5)	0.1285(7)	0.7605(11)	853(32)
C(16B)	0.1156(5)	0.3459(7)	0.5558(8)	861(33)
C(17B)	0.3012(3)	0,7367(5)	0.5922(6)	511(18)
C(18B)	0.2487(4)	0.8456(7)	0.5616(7)	737(30)
C(19B)	0.3667(3)	0.6929(6)	0.4733(6)	504(19)
C(20B)	0.4076(4)	0.7851(6)	0.4003(7)	691(27)
C(21B)	0.4675(5)	0.7435(75)	0.2913(9)	850(29)
C(22B)	0.4846(5)	0.6123(9)	0.2559(9)	871(33)
C(23B)	0.4440(5)	0.5181(8)	0.3286(9)	868(31)
C(24B)	0.3837(4)	0.5585(7)	0.4370(7)	673(24)

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TABLE II

Bond lengths (Å) and angles (deg) for **4d** (e.s.d.)

S(1)–O(1) = 1.440(4)	S(1)–O(2) = 1.445(4)
S(1)–C(1) = 1.780(6)	S(1)–C(1) = 1.817(7)
N(1)–C(6) = 1.411(6)	N(1)–C(7) = 1.263(5)
C(1)–C(2) = 1.371(7)	C(1)–C(6) = 1.405(6)
C(2)–C(3) = 1.385(10)	C(3)–C(4) = 1.376(8)
C(4)–C(5) = 1.374(8)	C(5)–C(6) = 1.388(8)
C(7)–C(8) = 1.518(7)	C(7)–C(12) = 1.514(85)
C(8)–C(9) = 1.574(9)	C(8)–C(13) = 1.559(7)
C(8)–C(16) = 1.479(11)	C(9)–C(10) = 1.502(14)
C(10)–C(11) = 1.507(10)	C(11)–C(12) = 1.550(7)
C(11)–C(13) = 1.524(9)	C(13)–C(14) = 1.528(8)
C(13)–C(15) = 1.540(7)	C(17)–C(18) = 1.521(10)
C(17)–C(19) = 1.514(7)	C(19)–C(20) = 1.340(7)
C(19)–C(24) = 1.359(9)	C(20)–C(21) = 1.358(9)
C(21)–C(22) = 1.359(14)	C(22)–C(23) = 1.382(10)
C(23)–C(24) = 1.407(10)	S(1B)–O(1B) = 1.434(5)
S(1B)–O(2B) = 1.440(4)	S(1B)–C(1B) = 1.776(4)
S(1B)–C(17B) = 1.806(5)	N(1B)–C(6B) = 1.411(5)
N(1B)–C(7B) = 1.255(8)	C(1B)–C(2B) = 1.386(6)
C(1B)–C(6B) = 1.414(7)	C(2B)–C(3B) = 1.378(9)
C(3B)–C(4B) = 1.381(9)	C(4B)–C(5B) = 1.351(7)
C(5B)–C(6B) = 1.391(8)	C(7B)–C(8B) = 1.513(7)
C(7B)–C(12B) = 1.514(9)	C(8B)–C(9B) = 1.554(9)
C(8B)–C(13B) = 1.549(10)	C(8B)–C(16B) = 1.517(9)
C(9B)–C(10B) = 1.530(15)	C(10B)–C(11B) = 1.549(12)
C(11B)–C(12B) = 1.535(9)	C(11B)–C(13B) = 1.529(10)
C(13B)–C(14B) = 1.527(9)	C(13B)–C(15B) = 1.515(9)
C(17B)–C(18B) = 1.506(10)	C(17B)–C(19B) = 1.524(7)
C(19B)–C(20B) = 1.373(9)	C(19B)–C(24B) = 1.376(9)
C(20B)–C(21B) = 1.398(10)	C(21B)–C(22B) = 1.347(12)
C(22B)–C(23B) = 1.384(13)	C(23B)–C(24B) = 1.396(18)
C(1)–S(1)–C(17) = 105.0(5)	O(2)–S(1)–C(17) = 107.2(4)
O(2)–S(1)–C(1) = 109.6(3)	O(1)–S(1)–C(17) = 109.46(3)
O(1)–S(1)–C(1) = 106.9(5)	O(1)–S(1)–O(2) = 118.0(5)
C(6)–N(1)–C(7) = 121.4(6)	S(1)–C(1)–C(6) = 120.6(6)
S(1)–C(1)–C(2) = 118.3(6)	C(2)–C(1)–C(6) = 121.1(7)
C(1)–C(2)–C(3) = 119.7(7)	C(2)–C(3)–C(4) = 119.7(8)
C(3)–C(4)–C(5) = 120.9(8)	C(4)–C(5)–C(6) = 120.5(7)
C(1)–C(6)–C(5) = 118.1(6)	N(1)–C(6)–C(5) = 121.2(6)
N(1)–C(6)–C(1) = 120.2(7)	N(1)–C(7)–C(12) = 128.8(6)
N(1)–C(7)–C(8) = 123.5(5)	C(8)–C(7)–C(12) = 107.7(5)
C(7)–C(8)–C(16) = 115.7(6)	C(7)–C(8)–C(13) = 100.9(6)
C(7)–C(8)–C(9) = 101.4(6)	C(13)–C(8)–C(16) = 120.5(7)
C(9)–C(8)–C(16) = 115.5(7)	C(9)–C(8)–C(13) = 99.8(6)
C(8)–C(9)–C(10) = 104.9(7)	C(9)–C(10)–C(11) = 103.4(7)
C(10)–C(11)–C(13) = 104.5(7)	C(10)–C(11)–C(12) = 105.5(6)
C(12)–C(11)–C(13) = 102.8(5)	C(7)–C(12)–C(11) = 100.4(5)
C(8)–C(13)–C(11) = 94.2(5)	C(11)–C(13)–C(15) = 114.5(6)
C(11)–C(13)–C(14) = 115.8(7)	C(8)–C(13)–C(15) = 112.9(6)
C(8)–C(13)–C(14) = 111.3(6)	C(14)–C(13)–C(15) = 107.8(7)
S(1)–C(17)–C(19) = 109.4(5)	S(1)–C(17)–C(18) = 108.2(6)
C(18)–C(17)–C(19) = 116.4(6)	C(17)–C(19)–C(24) = 120.1(5)
C(17)–C(19)–C(20) = 121.0(7)	C(20)–C(19)–C(24) = 118.9(6)
C(19)–C(20)–C(21) = 121.0(8)	C(20)–C(21)–C(22) = 120.0(7)
C(21)–C(22)–C(23) = 121.0(9)	C(22)–C(23)–C(24) = 118.5(9)

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TABLE II (*Cont'd*)

C(19)–C(24)–C(23)	120.5(7)
C(1B)–S(1B)–C(17B)	106.0(4)
O(2)–S(1B)–C(17B)	108.6(4)
O(2B)–S(1B)–C(1B)	106.9(4)
O(1B)–S(1B)–C(17B)	108.3(4)
O(1B)–S(1B)–C(1B)	108.5(4)
O(1B)–S(1B)–O(2B)	118.1(6)
C(6B)–N(1B)–C(7B)	119.4(5)
S(1B)–C(1B)–C(6B)	122.3(5)
S(1B)–C(1B)–C(2B)	118.3(6)
C(2B)–C(1B)–C(6B)	119.4(6)
C(1B)–C(2B)–C(3B)	120.8(7)
C(2B)–C(3B)–C(4B)	119.4(7)
C(3B)–C(4B)–C(5B)	120.7(8)
C(4B)–C(5B)–C(6B)	121.7(8)
C(1B)–C(6B)–C(5B)	118.0(6)
N(1B)–C(6B)–C(5B)	122.0(7)
N(1B)–C(6B)–C(1B)	119.9(6)
N(1B)–C(7B)–C(12B)	129.8(7)
N(1B)–C(7B)–C(8B)	123.6(6)
C(8B)–C(7B)–C(12B)	106.6(6)
C(7B)–C(8B)–C(16B)	115.4(7)
C(7B)–C(8B)–C(13B)	101.8(5)
C(7B)–C(8B)–C(9B)	102.6(6)
C(13B)–C(8B)–C(16B)	118.4(7)
C(9B)–C(8B)–C(16B)	114.2(7)
C(9B)–C(8B)–C(13B)	102.4(7)
C(8B)–C(9B)–C(10B)	103.7(7)
C(9B)–C(10B)–C(11B)	102.6(8)
C(10B)–C(11B)–C(13B)	102.6(7)
C(10B)–C(11B)–C(12B)	107.3(8)
C(12B)–C(11B)–C(13B)	103.5(7)
C(7B)–C(12B)–C(11B)	100.8(5)
C(8B)–C(13B)–C(11B)	93.2(6)
C(11B)–C(13B)–C(15B)	113.5(7)
C(11B)–C(13B)–C(14B)	114.6(7)
C(8B)–C(13B)–C(15B)	114.0(7)
C(8B)–C(13B)–C(14B)	111.7(7)
C(14B)–C(13B)–C(15B)	109.2(8)
S(1B)–C(17B)–C(19B)	107.2(5)
S(1B)–C(17B)–C(18B)	111.0(5)
C(18B)–C(17B)–C(19B)	115.1(6)
C(17B)–C(19B)–C(24B)	119.5(7)
C(17B)–C(19B)–C(20B)	120.7(7)
C(20B)–C(19B)–C(24B)	119.8(7)
C(19B)–C(20B)–C(21B)	120.1(8)
C(20)–C(21B)–C(22B)	120.2(8)
C(21B)–C(22B)–C(23B)	120.3(9)
C(22B)–C(23B)–C(24B)	119.8(9)
C(19B)–C(24B)–C(23B)	119.78

overnight at −20°C. Acetic anhydride and/or water (2 ml) was added, the layers separated, and the organic phase dried (anhydrous Na_2SO_4), concentrated and flash-chromatographed in a silica gel column eluting with gradients hexane-ethyl acetate.

4e (95% yield): oil. The four diastereoisomers (mixture 1:2:2:3) were separated into two pairs by flash chromatography eluting with petrol ether-ethyl acetate, 95:5. ^{1}H NMR of the mixture of four diastereoisomers (200 MHz, $CDCl_3$, TMS), δ (ppm): 0.87–1.32 (9H, s, four diast.), 1.37–2.00 (6H, series of m., four diast.), 2.06 (3H, s, one diast.), 2.10 (3H, s, one diast.), 2.11 (3H, s, one diast.), 2.14

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(3H, s, one diast.), 2.16–2.45 (4 diastereotopic H, series of m., four diast.), 5.36 (1H, d, J 3.7 Hz, one diast.), 5.45 (1H, d, J 4.6 Hz, one diast.), 5.66 (1H, d, J 10.0 Hz, one diast.), 5.68 (1H, d, J 11.0 Hz, one diast.), 6.43 (1H, d, J 3.7 Hz, one diast.), 6.45 (1H, d, J 11.0 Hz, one diast.), 6.65 (1H, d, J 11.0 Hz, one diast.), 6.80 (1H, d, J 3.7 Hz, one diast.), 6.57–8.12 (14H, series of m., four diast.), IR (KBr, pellets), ν_{max} 1671–1674 (C=N), 1308 (SO_2 asymm. stretch.), 1143 (SO_2 symm. stretch.) cm^{-1}. (Found: C, 73.2; H, 6.5; N, 2.5. $C_{32}H_{35}O_4NS$ requires C, 72.6; H, 6.7; N, 2.6%).

Hydrolysis of ketimine **4d**. Ketimine **4d** (155 mg, 0.392 mmol) in 2 ml of THF was heated at 60°C for 4 days with a 30% aqueous solution of citric acid (2.83 ml, 3.64 mmol). The solution was poured into water and extracted to give after crystallization from dichloromethane—petrol ether (1:1) amine **5** (3.84 mmol, 98% yield) m.p. 98–100°C, $[\alpha]^{25}$—160.31° (c = 0.95, $CHCl_3$). ^1H NMR (60 MHz, $CDCl_3$, TMS) δ (ppm): 1.73 (3H, d, J 7.0 Hz), 4.41 (1H, q, J 7.0 Hz), 4.83 (2H, broad s), 6.53–6.73 (3H, series of m), 7.11–7.44 (6H, series of m). IR (KBr, pellets), ν_{max} 3463 (NH_2), 3370 (NH_2). (Found: C, 64.8; H, 6.0; N, 5.6. $C_{14}H_{15}NO_2S$ requires C, 64.4; H, 5.8; N, 5.4%).

X-ray structure determination. Compound **4d** ($C_{24}H_{29}NO_2S$) crystallized in the triclinic P_1 space group with a = 14.284(2), b = 10.116(1), c = 8.490(1)Å; α = 108.3(1)°, β = 100.7(1)°, γ = 101.1(1)°; V = 1102.3Å^3; Z = 2, Dc = 1.19 gcm^{-3}. A number of 5138 unique reflections were read on Philips PW1100 ϑ–2ϑ scan mode to 2ϑ = 56° using MoKα monochromated radiation (λ = 0.7107 Å). The structure was phased by SHELX 86 programs and refined by blocked full matrix least squares using SHELX 76 programs. Thermal parameters of all non hydrogen atoms were anisotropic, hydrogen atoms were partially located on ΔF map but not refined. The final conventional R factor for the 3462 considered observed reflections [$I \geq 2.7\sigma(I)$] was 0.0489. Figure 1 shows a comparative view of the ORTEP drawings of the two conformers, while Figure 2 shows the crystal cell. Table I reports positional parameters and Table II bonds lengths (Å) and angles (deg) for each conformation.

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REFERENCES

1. O. De Lucchi, *Bull. Soc. Chim. Belg.*, **97**, 679 (1988); O. De Lucchi, M. Buso and G. Modena, *Tetrahedron Lett.*, **28**, 107 (1987); O. De Lucchi, V. Lucchini, C. Marchioro, G. Valle and G. Modena, *J. Org. Chem.*, **51**, 1457 (1986).
2. R. N. Prasad and K. Tietje, *Can. J. Chem.*, **44**, 1247 (1966); Y. Ishikawa, Y. Terao, K. Suzuki, N. Shikano and M. Sekiya, *Chem. Pharm. Bull.*, **32**, 438 (1984); C. Banzatti, P. Melloni and P. Salvadori, *Gazz. Chim. Ital.*, **117**, 259 (1987).
3. K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1570 (1971); D. P. Roelofsen and H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **91**, 605 (1972); J. M. McIntosh and P. Mishra, *Can. J. Chem.*, **64**, 726 (1986); U. Schöllkopf and R. Schütze, *Justus Liebigs Ann. Chem.*, 45 (1987).
4. J. M. McIntosh and K. C. Cassidy, *Can. J. Chem.*, **66**, 3116 (1988); J. M. McIntosh, R. K. Leavitt, P. Mishra, K. C. Cassidy, J. E. Drake and R. Chandha, *J. Org. Chem.*, **53**, 1947 (1988).
5. H.-J. Gais, J. Vollhardt, and H. J. Lindner, *Angew. Chem.*, **98**, 916 (1986); H.-J. Gais, J. Vollhardt, G. Hellmann, H. Paulus and H. J. Lindner, *Tetrahedron Lett.*, **29**, 1259 (1988).
6. L. Casella, G. Jommi, S. Montanari and M. Sisti, *Tetrahedron Lett.*, **29**, 2067 (1988); A. Alexakis, R. Sedrani, P. Mangeney and J. F. Normant, *Ibid.*, **29**, 4411 (1988).